

## Longitudinal Factor Analysis Reveals a Distinct Clustering of Cardiometabolic Improvements During Intensive, Short-Term Dietary and Exercise Intervention in Obese Children and Adolescents

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### Abstract

**Objective:** The aim of this study was to investigate changes in cardiometabolic clustering characteristics in response to highly significant weight loss.

**Background:** Pre–post analysis of a lifestyle intervention for the treatment of obesity and the assessment of interrelated metabolic changes were analyzed using principal component analysis (PCA). A total of  $n=75$  clinically obese boys and girls [standardized body mass index (sBMI)  $3.07 \pm 0.59$ ] aged 8–18 years were assessed after lifestyle intervention ( $30 \pm 12$  days).

**Results:** There were favorable improvements in BMI waist circumference, fasting insulin, triglycerides (TGs), systolic blood pressure (SBP) and diastolic blood pressure (DBP) (all  $P < 0.001$ ). PCA was performed using a simple conceptual model of changes in six metabolic variables: Overall and central obesity (BMI and waist circumference), dyslipidemia [TG and high-density lipoprotein cholesterol (HDL-C)], insulin resistance [fasting insulin or homeostasis model assessment of insulin resistance (HOMA-IR)], and blood pressure [SBP or mean arterial pressure (MAP)]. PCA models consistently identified two factors underlying the changes in six cardiometabolic variables. These were labeled a “metabolic” factor, typically including waist circumference, fasting triglyceride, insulin, or HOMA-IR and HDL-C (negatively) and an “obesity/blood pressure” factor, typically loading waist, BMI, SBP or MAP, and occasionally fasting insulin/HOMA-IR. The metabolic and obesity/blood pressure factors explained 26.5%–28.4% and 30.4%–31.9%, of the variance in metabolic risk factors changes, respectively. Reductions in BMI, waist circumference, and HOMA-IR (or fasting insulin) were central underlying features of cardiometabolic changes.

**Conclusion:** There were significant and favorable cardiometabolic risk factor changes to short-term weight-loss. A distinct clustering of cardiometabolic responses supports the etiological importance of both overall and central obesity and insulin resistance in the modification of cardiometabolic risk in obese youths.

### Introduction

INSULIN RESISTANCE AND HYPERINSULINEMIA were initially proposed as the important underlying construct associated with cardiometabolic clustering.<sup>1</sup> Subsequently, abdominal obesity has been strongly linked to fasting hyperinsulinemia, atherogenic dyslipidemia [reduced high density lipoprotein cholesterol (HDL-C), hypertriglyceridemia] and raised blood pressure.<sup>2</sup> Cardiometabolic clus-

tering is highly prevalent among obese children and adolescents.<sup>3</sup> However, the usefulness of the diagnostic term “metabolic syndrome” has been widely debated.<sup>4</sup> The construct of cardiometabolic risk is complicated by its physiological complexity and high degree of intercorrelation among cardiometabolic variables.<sup>5</sup> Exploratory factor analysis (EFA), a multivariate statistical data reduction technique, has been increasingly applied to summarize information from cardiometabolic variables to assess

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cumulative cardiometabolic risk<sup>6</sup> or specifically to examine the structure underlying the metabolic syndrome components within obese pediatric cohorts.<sup>7</sup>

However, only one study has used factor analysis techniques to examine prospective changes in cardiometabolic risk factors.<sup>8</sup> Previous studies have shown the robust nature of the linear relationships among derived "factors" over time within adolescents and emphasized its potential for assessing information about causal pathways within cardiometabolic clustering compared with cross-sectional analyses.<sup>6</sup> Long-term weight-loss reflected by sBMI changes, was tightly linked to changes in surrogate measures of insulin sensitivity and several cardiometabolic variables among obese adolescents.<sup>9</sup> To the best of our knowledge, no exploratory factor analysis has investigated the dynamic changes in cardiometabolic risk factors in clinically obese children and adolescents who have lost weight through an intensive exercise and dietary intervention. The aim of the present study was to examine of the pattern of change in cardiometabolic risk factors induced by a short-term intensive residential lifestyle intervention. The analytical structure of cardiometabolic clustering in obese children and adolescents utilizing different metabolic variable models will be explored.

## Methods

The obese children and adolescents were attendees of the Carnegie International Camp (CIC), a multifactorial residential summer weight loss program. This analysis includes 75 first-time attendees of the CIC who volunteered for blood sampling and completed both pre- and post intervention blood sampling. Data from 3 consecutive years (2004–2006) was used. Mainly British children and adolescents (8–18 years) attended and were recruited via self-parental referral, medical and social service referral, or educational organizations. Acceptance onto the weight-loss program was reliant on having a BMI >85<sup>th</sup> percentile.<sup>10</sup> There were no other inclusion criteria. The subjects were primarily Caucasians ( $n=72$ , Asian  $n=1$ , and black  $n=2$ ). Tanner development stages were not assessed.

Details of the program are reported elsewhere.<sup>11</sup> Briefly the CIC program incorporated dietary restriction, physical activity/exercise, and lifestyle education. The physical activity combined structured fun, skill-based activities consisting of six daily 1-h sessions. The dietary intervention provided sufficient daily energy to meet the individual's basal requirements adjusted for age and body mass. Energy intake ( $\text{kcal}\cdot\text{day}^{-1}$ ) was provided as three meals and a snack each day. Each child was assigned to one of four diet groups ranging from 1,050 to 3,050  $\text{kcal}\cdot\text{day}^{-1}$  based upon their age and body mass. The diet consisted of 15% protein, 30%–35% fat, and 50%–55% carbohydrate. A registered dietitian designed the diets. Each child underwent four 1-h obesity-related lifestyle educational sessions per week. Ethical approval was granted by Leeds West National Health Service Research Ethics Committee, Leeds, UK. All children and parents provided informed written assent/consent to participate.

### *Anthropometric and body composition measures*

Bioelectrical impedance analysis (BLA) assessed body mass using a Tanita TBF-310 (Tanita Corp, Tokyo, Japan). Height was measured to the nearest 0.1 cm using a floor-standing

Seca stadiometer (model 220). BMI was calculated ( $\text{weight}/\text{height}^2$ ), and sBMI was calculated using the cross-sectional stature and weight reference curves for the UK Waist was assessed at the midpoint (narrowest point between the lowest rib and the iliac crest) to the nearest 0.1 cm using an inflexible tape measure. Blood pressure was measured using a mercury sphygmomanometer (Mercurial BK1001) on the left arm. All subjects sat quietly for 5 min prior to measurement. A single measurement was taken in the semisupine position. In a subsample of participants (2006 cohort), a digital blood pressure monitoring device as opposed to manual method was used (Omron HEM-773AC, UK). Measurement protocols defined the appropriate cuff size to be used in all measurements.

### *Biochemical measurements*

Fasting blood samples (12–13.5 h) were drawn by venipuncture. Analyses for lipoprotein-lipids, glucose, and insulin were undertaken using routine clinical analyses within the Department of Clinical Biochemistry, Leeds General Infirmary, UK. Serum HDL-C was determined by an elimination and catalase procedure. Fasting insulin concentration was analyzed by an ADVIA sandwich immunoassay using chemiluminescent technology. The intraassay coefficient of variation for plasma insulin was 3.5%. Plasma apolipoprotein B (apo B) was measured by an enzyme-linked immunosorbent assay (ELISA) technique. The within-batch coefficient of variation for apoB was 8.7% and the between-batch coefficient of variation was 9.9% and was measured in the Specialist Assay Laboratory, Clinical Biochemistry, Manchester Royal Infirmary.

### *Statistical analysis*

All variables were assessed for normality of distribution. Paired-sample *t*-tests were used to determine mean differences for pre-post intervention metabolic variables. Pearson correlation coefficients were used to assess the relationships between continuous variables. PCA was applied to longitudinal changes in cardiometabolic variables. The four EFA models evaluated were distinguished by the main components of the metabolic syndrome. This included, overall and central obesity measures (BMI, waist circumference), dyslipidemia (TGs and HDL-C), and a single measure of blood pressure (systolic or mean arterial pressure) and marker of insulin resistance [fasting insulin or homeostasis model assessment (HOMA)]. All models included BMI and waist circumference, combined with four other metabolic variables. These included two lipoprotein-lipid markers (TG, HDL-C), one insulin resistance (IR) marker (fasting insulin or HOMA-IR), and one blood pressure component [systolic blood pressure (SBP) or mean arterial blood pressure (MAP)]. EFA involves three procedures: (1) Extraction of factors; (2) rotation of factors to facilitate interpretation of the latent factors identified; and (3) naming and interpretation of each underlying factor based on the estimated values for the factor loadings.<sup>12</sup>

The Kaiser-Meyer-Olkin (KMO) statistic was used as a measure of sampling adequacy, and the Bartlett test of sphericity was used as a measure of the ability to perform a factor analysis.<sup>5</sup> The KMO statistic varies from 0 to 1.0, and an overall KMO of 0.60 or higher (preferably above 0.7) indicates suitability of the data for factor analysis based on the correlations and partial correlations among metabolic variables. Furthermore, communality statistics were examined to

assess the 'reliability' of the metabolic risk variables in each analysis. PCA transforms the original variables into 'factors' that are uncorrelated and account for decreasing proportions of the variance of the data. Factors with a variance or eigenvalue  $>1.0$  were retained for inspection.

Previously, the process of factor rotation and selection of thresholds for factor loading has been arbitrary, but may importantly affect the results and their interpretation.<sup>12</sup> Accordingly, we compared different rotational techniques to facilitate the interpretation of factors. We used the orthogonal varimax rotation method. However, direct oblimin, an oblique rotation technique, was initially used in all analyses as a filter technique. Following oblique rotation, the factor (component) correlation matrix was examined. Small correlations amongst identified factors ( $<0.32$ , corresponding to 10% explained variance) were considered as supporting orthogonality in the model. Each factor was characterized by its loading or correlation with the original metabolic variables, which, in this study, included the metabolic changes over time. Factor loadings  $\geq 0.4$  were retained and interpreted as the contribution of that metabolic variable to the specific factor. Conventionally, variables that have a factor loading of 0.4 or greater are considered to load on a factor. Variables were considered to have potential loading if correlation coefficients were  $>0.3$ . All analyses were conducted using SPSS version 17.0 (Chicago, IL).

## Results

The lifestyle intervention lasted a mean of  $30 \pm 12$  days (range 45 days), and produced a significant loss of body mass, BMI, waist circumference, total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C), HDL-C, TG, insulin, glucose, HOMA-IR, and SBP and DBP (all  $P < 0.001$ ; see Table 1). Pearson correlations showed that changes in measures of obesity (BMI and waist) were significantly (all  $P < 0.05$ ) positively associated with changes in SBP or MAP (all  $r = 0.32$ – $0.37$ ). Changes in waist circumference were more strongly related to changes in fasting insulin and HOMA-IR ( $r = 0.43$  and  $0.44$ , respectively) than BMI (both  $r = 0.29$ ).

Waist circumference correlated positively with TGs ( $r = 0.34$ ,  $P < 0.05$ ). Changes in fasting insulin concentration and HOMA-IR correlated positively with changes in TGs ( $r = 0.43$ ,  $P < 0.01$ ). Blood pressure measures were not significantly related to changes in markers of insulin resistance. In all EFA undertaken with six metabolic variables, the Bartlett test of sphericity was significant (chi-squared values ranging from approximately  $\chi^2 = 71.6$ ,  $P < 0.001$  to  $\chi^2 = 78.0$ ,  $P < 0.001$ , respectively). The overall KMO statistic (a measure of sampling adequacy) was consistent at 0.7, indicating good suitability of the longitudinal change data for factor analysis. Four separate PCAs were undertaken, entering six metabolic variables into exploratory PCA models (Table 2). These models consistently identified two underlying factors and explained approximately 58% of the data variance. Preliminary oblique factor rotations showed correlations of less than  $\pm 0.26$  between the two factors identified, indicating suitability of orthogonal rotation to produce two unrelated factors.

The first uncorrelated factor was characterized by positive correlation coefficients (loadings  $<0.75$ ) with waist circumference and BMI with either SBP or MAP and, in several analyses, a lower loading of fasting insulin or HOMA-IR (correlation coefficients of  $>0.3$ – $0.40$ ). We labeled this factor as "obesity/blood pressure." The second factor was characterized as a "metabolic" factor, where changes in the lipid factors (TG  $>0.8$  and negatively HDL-C greater than  $-0.5$ ) were correlated with changes in central obesity (WC,  $>0.3$ – $0.4$ ) and fasting insulin or HOMA-IR (correlation coefficients of  $>0.50$ ). Notably, within three of the four EFAs entering six variables, waist circumference and a surrogate measure of insulin resistance (fasting insulin or HOMA-IR) loaded together on both underlying factors (Table 2).

## Discussion

The present study is the first to report longitudinal changes in cardiometabolic risk factors and their clustering characteristics in obese children and adolescents during an intensive residential weight loss intervention. Previous

TABLE 1. ANTHROPOMETRIC, BODY COMPOSITION, AND CARDIOMETABOLIC CHANGES FOLLOWING ACUTE WEIGHT LOSS IN OBESE CHILDREN AND ADOLESCENTS

	n	Pre Mean $\pm$ SD	Post Mean $\pm$ SD	P value
Body mass (kg)	75	94.2 $\pm$ 22.1	88.8 $\pm$ 20.7	<0.001
BMI ( $\text{kg} \cdot \text{m}^{-2}$ )	75	34.2 $\pm$ 6.4	32.1 $\pm$ 6.0	<0.001
sBMI	75	3.07 $\pm$ 0.59	2.82 $\pm$ 0.63	<0.001
Waist circumference (cm)	73	98.4 $\pm$ 12.0	92.9 $\pm$ 10.7	<0.001
SBP (mmHg)	73	120 $\pm$ 13	116 $\pm$ 11	<0.01
DBP (mmHg)	72	72 $\pm$ 10	68 $\pm$ 10	<0.05
TC ( $\text{mmol} \cdot \text{L}^{-1}$ )	75	4.15 $\pm$ 0.69	3.27 $\pm$ 0.58	<0.001
LDL-C ( $\text{mmol} \cdot \text{L}^{-1}$ )	75	2.48 $\pm$ 0.57	1.80 $\pm$ 0.45	<0.001
HDL-C ( $\text{mmol} \cdot \text{L}^{-1}$ )	75	1.20 $\pm$ 0.24	1.11 $\pm$ 0.23	<0.001
TC/HDL-C ratio	75	3.55 $\pm$ 0.74	2.99 $\pm$ 0.60	<0.001
TG ( $\text{mmol} \cdot \text{L}^{-1}$ )	75	1.11 $\pm$ 0.49	0.84 $\pm$ 0.31	<0.001
Apo B ( $\text{mg} \cdot \text{dL}^{-1}$ )	73	89.3 $\pm$ 21.8	69.3 $\pm$ 16.9	<0.001
Glucose ( $\text{mmol} \cdot \text{L}^{-1}$ )	74	4.79 $\pm$ 0.40	4.55 $\pm$ 0.31	<0.001
Insulin ( $\text{mU} \cdot \text{L}^{-1}$ )	74	17.5 $\pm$ 11.1	12.6 $\pm$ 7.7	<0.001
HOMA-IR	73	3.7 $\pm$ 2.5	2.6 $\pm$ 1.7	<0.001

SD, standard deviation; BMI, body mass index; sBMI, standardized BMI; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; Apo B, apolipoprotein B; HOMA-IR, homeostasis model assessment of insulin resistance.

TABLE 2. SUMMARY TABLE OF FOUR PCA ROTATED COMPONENT MATRIX (VARIMAX ROTATION) MODELS OF CHANGES IN SIX METABOLIC VARIABLES FOLLOWING ACUTE WEIGHT LOSS IN OBESE CHILDREN AND ADOLESCENTS

		<i>Factors, metabolic variable loadings, and factor variance</i>	
		<i>Obesity/blood pressure</i>	<i>Metabolic</i>
Metabolic variables entered			
WC	WC	<b>0.769</b>	<b>0.371</b>
BMI	BMI	0.785	
TG	TG		0.814
HDL-C	HDL-C		-0.653
HOMA-IR	HOMA-IR	<b>0.376</b>	<b>0.584</b>
MAP	MAP	0.726	
Variance explained (%)		31.3	26.7
WC	WC	<b>0.783</b>	<b>0.353</b>
BMI	BMI	0.772	
TG	TG		0.815
HDL-C	HDL-C		-0.665
HOMA-IR	HOMA-IR	<b>0.408</b>	<b>0.559</b>
SBP	SBP	0.732	
Variance explained (%)		31.9	26.5
WC	WC	<b>0.774</b>	<b>0.416</b>
BMI	BMI	0.779	
TG	TG		0.833
HDL-C	HDL-C		-0.577
Insulin	Insulin	<b>0.309</b>	<b>0.676</b>
MAP	MAP	0.753	
Variance explained (%)		30.4	28.4
WC	WC	<b>0.730</b>	<b>0.449</b>
BMI	BMI	0.752	
TG	TG		0.839
HDL-C	HDL-C		-0.536
Insulin	Insulin		0.695
SBP	SBP	0.774	
Variance explained (%)		30.4	28.4

Variables with factor loadings >0.3 are listed and variables loading on both factors are highlighted in bold.

PCA, principal component analysis; WC, waist circumference; BMI, body mass index; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; MAP, mean arterial pressure; SBP, systolic blood pressure.

studies have typically applied EFA within cross-sectional studies of obese youths or only reported separate metabolic changes or dichotomized 'metabolic syndrome' phenotypes.<sup>13-16</sup> Therefore, distinct features of the present study include: (1) a group of clinically obese children and adolescent participants who significantly reduced body mass and waist circumference; (2) a standardized lifestyle intervention with largely comparable dietary and physical activity modifications undertaken by all participants; (3) statistically and clinically significant reductions in several cardiometabolic variables (fasting lipoprotein-lipids, glucose, insulin, and blood pressures) not confounded by the effects of smoking, alcohol, or medications; (4) application of different EFA techniques for data reduction of cardiometabolic responses, with due consideration of variable selection and satisfactory evidence of sampling adequacy and variable communality.

Weiss et al.<sup>9</sup> showed that sBMI changes were significantly and negatively correlated with changes in insulin sensitivity and positively with glucose and lipoprotein-lipid responses. Longer-term sustained weight loss also demonstrated improvement in insulin sensitivity measures and lipoprotein-lipid profile responses in prepubertal obese children.<sup>17</sup> In contrast, a retrospective case series of 207 obese children and adolescents following 12 weeks of lifestyle intervention showed that reductions in obesity measures were not asso-

ciated with corresponding reductions in metabolic measures.<sup>18</sup>

Several cross-sectional studies have applied PCA to childhood and adolescent datasets, including obese cohorts, and have indicated that the 'insulin resistance syndrome' was a clinically recognizable entity with multiple pathophysiological mechanisms (reflected by between two and five underlying factors). However, studies have been inconsistent in terms of the metabolic variables considered, the precise PCA techniques employed to interpret factors, and statistical approaches adopted. Indeed, reports outlining more than two underlying factors have included as separate metabolic variables: (1) from 5 up to 16 metabolic variables simultaneously; (2) considered both arterial (SBP and DBP) blood pressure<sup>6</sup>; and (3) fasting and post oral glucose tolerance test concentrations.<sup>7,13,19</sup> Furthermore, interpretation of factors has been complicated by consideration of TC or LDL-C in some analyses.<sup>6</sup>

Providing clarification of the role of surrogate markers of insulin resistance (fasting insulin and HOMA) and obesity measures (raw or standardized BMI, waist circumference, and body fat content) within cardiometabolic clustering has been implicit in earlier studies. Recent cross-sectional confirmatory factor analysis findings in children and adolescents<sup>19,20</sup> have shown the potential usefulness of simple

conceptual models using standard clinic-based anthropometric measures. Our findings indicated that the pattern of change in the components of the metabolic syndrome observed during an acute weight loss intervention setting can be reduced to two underlying factors by considering six clinically relevant variables to represent the components of the metabolic syndrome. Two underlying pathophysiological constructs were most consistently extracted from the metabolic intercorrelations within our longitudinal analysis incorporating up to six metabolic variables. We termed these "metabolic" and "obesity/blood pressure" factors.

Our "metabolic factor" findings are broadly consistent with several early EFA studies using orthogonal rotation which revealed five metabolic variables (ponderal index, HDL-C, TG, fasting insulin, and glucose) linked on one underlying "metabolic" factor.<sup>16</sup> In the above analysis, a separate factor identified was characterized by both blood pressures and insulin concentration. These clustering features were reported to be independent of sex and evident within childhood (5–11 years) and adolescent (12–17 years) groups. The above investigators highlighted the key linking of a metabolic factor (hyperinsulinemia, dyslipidemia, and obesity) to hypertension through shared correlation with hyperinsulinemia/insulin resistance. Notably, two studies have undertaken PCA on metabolic clustering within selected larger cohorts of obese children and adolescents. Interestingly, Weiss et al.<sup>13</sup> revealed three correlated factors (using an oblique rotation technique) of obesity/glucose metabolism, dyslipidemia, and blood pressure. A strong loading of insulin resistance (fasting HOMA-IR) to the obesity/glucose factor and "moderate loading" to the dyslipidemia factor was interpreted to indicate a component of insulin resistance underlying two of three factors that accounted for the majority of the variance in the dataset.

LaFortuna et al.<sup>7</sup> showed that PCA with orthogonal varimax rotation reduced 11 correlated metabolic variables to four uncorrelated factors in boys; these included obesity/hypertension, dyslipidemia, and insulin resistance and hyperglycemia factors. Notably, obesity and fat distribution variables also loaded significantly onto the dyslipidemia and insulin resistance factors. In obese girls, no similar commonalities were evident. However, few previous studies have examined how the various factors change together over time and neither study examined the effects of an active intervention.<sup>6,8</sup>

Among our obese children and adolescents, combined changes in waist circumference and fasting insulin/HOMA-IR appeared central to most of these underlying factors. This provides further support for the hypothesis that the different dimensions of metabolic clustering or indeed the metabolic syndrome are linked through abdominal obesity and markers of insulin resistance. Our findings of central adiposity and insulin sensitivity modulating cardiometabolic risk in obese adolescents are consistent with other investigations using different research designs and statistical approaches.<sup>21</sup> Cross-sectional findings from the Bogalusa Heart Study have shown the use of both BMI and waist circumference for the prediction of metabolic clustering among children and adolescents has significant clinical utility.<sup>22</sup>

The results of metabolic clustering using EFA should be interpreted with some caution, given that it is not, strictly speaking, a hypothesis-testing technique. Our study indicates that important relevant information has been omitted

from numerous earlier reports and several arbitrary decisions are therefore necessarily made when using this approach. Some relevant issues have previously been reviewed,<sup>23</sup> and our analysis adds to the conceptual understanding of this multivariate correlational technique in the context of metabolic clustering in obese children and adolescents. In our study, the number of participants is relatively small, and we were not able to run separate analyses to account for differences in metabolic responses to weight loss intervention in obese boys and girls. Furthermore, we were not able to consider the effect of differences in sexual maturity within this cohort.

In summary, despite the relatively small size of the study, we have shown very favorable cardiometabolic risk factor modifications and a distinct clustering of metabolic responses to short-term, lifestyle-induced, weight loss. Given the rapidly growing literature on the prevalence, outcomes, and underlying pathophysiology of the metabolic syndrome, we consider that our findings provide a further contribution to the understanding of this common metabolic phenotype in obese children and adolescents.

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### Author Disclosure Statement

No competing financial interests exist.

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